AF/1647

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In re application of	:	Goddard, et al.
Appl. No.	:	10/063,578
Filed	:	May 3, 2002
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Rachel Kapust Hunnicutt
Art Unit	:	1647

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

August 5, 2005
(Date)

AnneMarie Kaiser, Reg. No. 37,649

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an Appellants' Brief to the Board of Patent Appeals:

FEE CALCULATION				
FEE TYPE		**FEE CODE**	**CALCULATION**	**TOTAL**
Appeal Brief	*41.20(b)(2)*	1402 ($500)		$500
1 Month Extension	*1.17(a)(1)*	1251 ($120)		$120
			TOTAL FEE DUE	$620

(X) An extension of time is hereby requested by payment of the appropriate fee indicated above.

(X) A copy of evidence cited in Appellant's Brief and listed in Appendix B.

(X) An Amendment After Final Office in 3 pages is enclosed.

(X) A check in the amount of $620 to cover the foregoing fees is enclosed.

(X) If applicant has not requested a sufficient extension of time and/or has not paid any other fee in a sufficient amount to prevent the abandonment of this application, please consider this as a Request for an Extension for the required time period and/or authorization to charge our Deposit Account No. 11-1410 for any fee which may be due. Please credit any overpayment to Deposit Account No. 11-1410.

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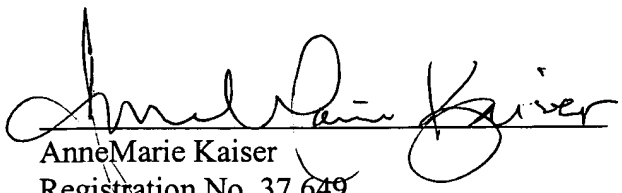

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant	:	Goddard, et al.
Appl. No.	:	10/063,578
Filed	:	May 3, 2002
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Rachel Kapust Hunnicutt
Group Art Unit	:	1647

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

August 5, 2005
(Date)

AnneMarie Kaiser, Reg. No. 37,649

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANT'S BRIEF

Mail Stop Appeal Brief – Patents
COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Applicants appeal the rejection of Claims 1-5 in the above-captioned patent application. These claims were rejected in a Final Office Action dated January 13, 2005. Additional arguments were made and additional references were cited by the Examiner in an Advisory Action dated April 12, 2005. Applicants filed a Notice of Appeal May 11, 2005. Applicants file concurrently herewith an Amendment After Final Office Action, and a request for a 1-month extension of time.

08/08/2005 JBALINAN 00000082 10063578
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I. REAL PARTY IN INTEREST

Pursuant to 37 C.F.R. 41.37(c)(1), Appellants hereby notify the Board of Patent Appeals and Interferences that the real party in interest is the assignee of record for this application, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

08/08/2005 JBALINAN 00000082 10063578
02 FC:1251 120.00 OP

II. RELATED APPEALS AND INTERFERENCES

A Notice of Appeal was filed in the related Application No. 10/063584, and the Appeal Brief was filed on July 27, 2005. Appellants are unaware of any other related appeals or interferences.

III. STATUS OF THE CLAIMS

The above-captioned application was filed with Claims 1-6. Claim 6 was canceled in an Amendment and Response to Office Action mailed November 23, 2004. Claims 1-5 were finally rejected by the Examiner in a final Office Action mailed January 13, 2005. Accordingly, Claims 1-5 are the subject of this appeal. The claims are attached hereto as Appendix A.

IV. STATUS OF AMENDMENTS

Appellants filed a "Response to Final Office Action" on March 11, 2005, submitting the claims with no additional amendments, and offering additional evidence in support of Appellants' arguments. In an Advisory Action mailed April 12, 2005, the Examiner indicated that the arguments and affidavit or other evidence would be entered for purposes of appeal. Appellants file concurrently herewith an Amendment After Final Office Action amending Claim 1 to recite an "isolated antibody." Accordingly, Claims 1-5 are the subject of this appeal. The claims attached hereto as Appendix A reflect the claims as amended by the Amendment After Final Office Action filed concurrently herewith.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter relates to isolated antibodies which specifically bind to the polypeptide having SEQ ID NO: 68. As recited in the Appendix A, independent Claim 1 reads:

1. An isolated antibody that specifically binds to the polypeptide of SEQ ID NO: 68.

Various aspects of the claimed antibody are described in the specification at, for example, paragraphs [0024], [0225],[0238]-[0248], and [0361]-[0405]. SEQ ID NO: 68 is disclosed in the Sequence Listing appended to the application.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Examiner has rejected Claims 1-5 under 35 U.S.C. §101, stating that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The Examiner has also rejected Claims 1-5 under 35 U.S.C. §112, first paragraph. The Examiner asserts that since the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art clearly would not know how to use the claimed invention.

VII. APPELLANTS' ARGUMENT

A. Utility Rejection

The first issue before the Board is whether Appellants have asserted at least one "specific, substantial, and credible utility." *See* Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001). Appellants have asserted that the claimed antibodies to the polypeptide of SEQ ID NO: 68 (the PRO1158 polypeptide) are useful as diagnostic tools for cancer, particularly for lung cancer. This asserted utility is specific, substantial, and credible.

Briefly stated, Appellants' asserted utility is based on the disclosure in Example 18 of the instant application that the mRNA encoding the PRO1158 polypeptide is more highly expressed in normal lung tissue compared to lung tumor tissue. It is well-established that there is a reasonable correlation between changes in mRNA level for a particular gene and a corresponding change in the level of expression of the encoded polypeptide, such that increasing or decreasing the amount of mRNA for a particular gene leads to a corresponding increase or decrease in the amount of the encoded protein. Thus, one of skill in the art would be more likely than not to believe that, like the PRO1158 mRNA, the PRO1158 protein is more highly expressed in normal lung tissue compared to lung tumor tissue. This differential expression of PRO1158 polypeptide is useful for distinguishing lung tumor tissue from normal lung tissue. Therefore, the claimed antibodies to the PRO1158 polypeptide have a specific, substantial and credible utility as diagnostic tools for cancer, particularly lung cancer, as is explained in more detail below.

1. ***Utility – Legal Standard***

A "specific utility" is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." *See M.P.E.P.* § 2107.01 I. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an Appellant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." *M.P.E.P.* § 2107.01 (emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the Appellant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the Appellant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A.

2. ***Utility – Burden of Proof***

It is well established that a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented "must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is reason

for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). Thus "the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Appellant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *Id.*

3. ***Utility – Standard of Proof***

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he Appellant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the Appellant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (emphasis in original, citations omitted).

The Court of Appeals for the Federal Circuit has stated that the standard for satisfying the utility requirement is a low one:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *See Brenner v. Manson,* 383 U.S. 519, 534, 86 S.Ct. 1033, 16 L.Ed.2d 69 (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger,* 120 F. 274, 275 (7th Cir.1903) (test for utility is whether invention "is incapable of serving any beneficial end"). *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q. 2d 1700 (Fed. Cir. 1999) (emphasis added).

The low threshold for satisfying the utility requirement is reflected in the standard set by the Federal Circuit for invalidating a patent based on a lack of utility: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack

of utility. Some degree of utility is sufficient for patentability. Further, the defense of non-utility cannot be sustained without proof of total incapacity." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 U.S.P.Q. 473 (Fed. Cir. 1984) (emphasis added, citations omitted).

Because the standard for satisfying the utility requirement is so low, requiring total incapacity for a finding of no utility, the M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been *rarely* sustained by federal courts. Generally speaking, in these *rare* cases, the 35 U.S.C. 101 rejection was sustained [] because the Appellant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967) (underline emphasis in original, italic emphasis added).

4. ***Appellants Asserted a Specific, Substantial and Credible Utility that is Sufficient to Satisfy the Utility Requirement of § 101***

The claimed subject matter relates to antibodies which specifically bind to the polypeptide having SEQ ID NO: 68. The polypeptide of SEQ ID NO: 68 (referred to as "PRO1158 polypeptide") is encoded by the polynucleotide of SEQ ID NO: 67 (also referred to as DNA60625-1507). *Specification* at ¶¶ [0093-0094]. Appellants have asserted that the claimed antibodies are useful as diagnostic tools for cancer, particularly lung cancer.

In "Example 18: Tumor Versus Normal Differential Tissue Expression Distribution" Appellants disclose that the mRNA encoding PRO1158 polypeptide is more highly expressed in normal lung tissue compared to lung tumor. *Specification* at ¶¶ [0529-0530] and accompanying tables. As explained in paragraph [0530], the differential expression of the PRO1158 mRNA was detected using the well-established technique of quantitative PCR amplification of cDNA libraries isolated from different human normal and tumor tissue samples. To ensure that equivalent amounts of nucleic acid were used in each reaction, the cDNA for β-actin was used as a control.

The specification teaches that identification of the differential expression of a PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type "renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor." *Specification* at ¶ [0530]. Similarly, Appellants disclose that PRO polypeptides "may also be

used diagnostically for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type." *Specification* at ¶ [0336]. Likewise, Appellants disclose the use of antibodies to PRO polypeptides as diagnostic tools:

> [A]nti-PRO antibodies may be used in diagnostic assays for PRO [polypeptide], *e.g.*, detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases. *Specification* at [0407].

Taken together, the specification clearly discloses the use of the claimed antibodies as diagnostic tools for cancer, particularly lung cancer. This utility is substantial, as one of skill in the art will recognize that the diagnosis of cancer is a "real world" use; it is specific, as the diagnosis of lung cancer is not a utility that applies to the broad class of antibodies; and it is credible, as it not a utility "that could only be true if it violated a scientific principle, ...or a law of nature, or [is] wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967). Because Appellants' specification contains a disclosure of utility which corresponds in scope to the claimed subject matter, the asserted utility "must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). Therefore, the burden of establishing a *prima facie* case of lack of utility rests with the PTO. *See, In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) ("the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure").

5. *The Examiner's Unsupported Arguments*

To establish a *prima facie* showing that the claimed subject matter lacks utility, the Examiner must "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Examiner has filed a first Office Action, final Office Action, and an

Advisory Action during the prosecution of the instant application. None of these papers provide any evidence that one of ordinary skill in the art would reasonably doubt the asserted utility.

In the first Office Action, dated August 24, 2004, the Examiner rejected the pending claims, stating "Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." *First Office Action* at 3. The Examiner stated that "[t]he antibodies of the current invention bind to polypeptides comprising SEQ ID NO: 68. However, there is no utility for a polypeptide comprising SEQ ID NO: 68." *Id.* The Examiner rejected several of the disclosed utilities for the claimed antibodies, including therapeutic uses of the antibodies, stating that "the specification does not disclose any diseases or conditions known to be associated with the encoded PRO 1158 polypeptide. Further research would be required to identify a disease in which the encoded polypeptide is involved." *Id.* at 3. The Examiner did not address the asserted utility of a diagnostic tool for cancer.

In a final Office Action dated January 13, 2005, the Examiner maintained her rejection of the pending claims "for the reasons of record." The Examiner stated that Appellants' arguments made in an Amendment and Response to Office Action filed November 23, 2004, were fully considered, but were not persuasive. First, the Examiner argued that the data of Example 18 and a declaration entered to support the data were insufficient because they did not indicate how high the levels of expression were, how reproducible and reliable the results were, whether the results were statistically significant, or the nature or number of samples used. *Final Office Action* at 4. The Examiner concluded that the disclosure "does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any disease." *Id.*

The Examiner also argued that paragraph 4 of the second Grimaldi declaration (originally submitted as Exhibit 2) was not persuasive because unlike the genes discussed in the references cited in the declaration "The PRO1158 gene, ... has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, ... no translocation of PRO1158 is known to occur. ... No mutation or translocation of PRO1158 has been associated with lung cancer." *Final Office Action* at 4. The Examiner concluded that "[i]n the absence of any of the above information" the disclosure was insufficient to satisfy the requirements of § 101.

Finally, the Examiner stated that whether or not increased levels of PRO1158 mRNA correlate with increased levels of PRO1158 protein is not an issue. The Examiner stated that the declarations and cited references "do not establish a substantial utility for the claimed PRO1158 nucleic acid molecules. As stated above, the specification does not provide sufficient guidance to the skilled artisan to diagnose or treat any disease. Thus, there would be no specific utility for antibodies which bind to PRO1158 proteins." *Final Office Action* at 5.

In response to the final Office Action, Appellants submitted a Response to Final Office Action, mailed March 11, 2005, which included additional arguments and references in support of their initial Amendment. The Examiner issued an Advisory Action on April 12, 2005.

In the Advisory Action, the Examiner essentially repeated her pervious unsupported arguments, stating that Appellants had not taught what kind of tumors could be diagnosed, the baseline levels of expression, or provided numerical values for the levels of overexpression and underexpression. The Examiner argued that "[m]erely stating that the nucleic acid is 'more highly expressed' is simply an invitation to experiment," and one of skill in the art would not know how to use the claimed invention to diagnose tumors. *Advisory Action* at 2.

In response to Appellants' arguments, declarations, and references stating that in general, there is a positive correlation between changes in mRNA and changes in the level of the encoded polypeptide, the Examiner cited Chen *et al.* (*Molecular and Cellular Proteomics*, 1:304-313 (2002)) for the first time. The Examiner argued that Chen *et al.* teach "that correlation between protein levels and mRNA expression in lung adenocarcinomas varies depending upon the protein." *Advisory Action* at 2. Based on Chen, the Examiner concluded that "without further testing it cannot be assumed that mRNA levels correlate to protein levels." *Id.*

6. ***The Examiner has not established a Prima Facie case that Claims 1-5 lack Utility***

The above arguments do not satisfy the Examiner's burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Examiner has the burden of presenting "countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the Appellant's assertion of utility." *M.P.E.P.* at §2107.02 III.A., *citing*

in re Brana, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Appellant to provide rebuttal evidence") (emphasis added). With the exception of the Chen *et al.* reference cited for the first time in the Advisory Action, the Examiner's assertions are not supported by any facts or evidence, and as is explained below, Chen does not support the Examiner's position. Therefore there is simply no evidence in the record to support her assertion that the disclosure "does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any disease." Absent some evidence to support her assertions, the Examiner has failed to establish a *prima facie* showing that one of skill in the art would reasonably doubt the asserted utility, and the Board should accept Appellants' disclosed utility as sufficient.

a. *The data in Example 18 are sufficient to establish the asserted utility*

Appellants turn first to the Examiner's arguments challenging the reliability of the data reported in Example 18. The Examiner argues that Example 18 and the first declaration of Mr. Grimaldi are insufficient to overcome the utility rejection of the pending claims because they do not teach how high the expression level is, what the level of reproducibility or reliability of the data is, whether the results are statistically significant, or the nature or number of samples that were used. *Final Office Action* at 4; *Advisory Action* at 2. The Examiner concludes that the disclosure would not enable one of skill in the art to differentiate amongst expression levels to diagnose any disease. *Final Office Action* at 4. None of these unsupported arguments are sufficient to establish a *prima facie* case that one of skill in the art would reasonably doubt the asserted utility.

The gene expression data in Example 18 of the specification show that the mRNA associated with protein PRO1158 was more highly expressed in normal lung tissue compared to lung tumor. *See Specification* at ¶ [0530] and accompanying tables. Gene expression was analyzed using standard quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. *Id.* It is well known in the art that the number of copies of a particular cDNA in the cDNA library is determined by the number of copies of the corresponding mRNA in the sample. Therefore, the cDNA libraries can be used to determine the level of expression of the corresponding mRNA in the tissue.

Appellants have asserted that identification of the differential expression of the PRO1158 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. *Id.* In support of this asserted utility, Appellants submitted as Exhibit 1 to their Amendment and Response to Office Action a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue. *See First Grimaldi Declaration.*

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." *First Grimaldi Declaration* at ¶ 7.

This declaration makes clear that since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, how high the level of expression in normal tissue is, is irrelevant. As to the Examiner's questions about the reliability and reproducibility of the results, Appellants employed standard techniques which are well-known and accepted by those of skill in the art. Mr. Grimaldi states that if a difference is detected using these techniques, "this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes..." *Id.* Thus, it is the uncontested opinion of an expert in the field that the results are reliable enough to indicate that the claimed antibodies are useful as diagnostic tools. As to the Examiner's concerns regarding the number and types of samples used, Mr. Grimaldi states that the samples are pooled samples of normal and tumor tissue. *Id.* at ¶ 5.

Finally, the Examiner has rejected the data because she questions the statistical significance of the data. However, Appellants are not required to prove utility to a statistical

certainty, only that it is more likely than not true. *See Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 U.S.P.Q. 881, 883-84 (C.C.P.A. 1980) (reversing the Board and rejecting an argument that evidence of utility was insufficient because it was not statistically significant). Therefore, whether the results are statistically significant or not is irrelevant to establishing the asserted utility.

The data in Example 18 and the first Grimaldi Declaration are therefore sufficient to establish the asserted utility, and the Examiner has not rebutted the presumption of utility that the Appellants' application is afforded. Mr. Grimaldi is an expert in the field who conducted or supervised the experiments at issue. His declaration is based on personal knowledge of the relevant facts at issue. Appellants' have reminded the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." *M.P.E.P.* § 2107 (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *See in re Alton* 76 F.3d 1168 (Fed. Cir. 1996). The Examiner has offered no reason or evidence to reject either the underlying data or Mr. Grimaldi's conclusions. Therefore, the Examiner should accept Mr. Grimaldi's opinion with regard to his statement that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal."

In conclusion, Appellants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1158 cDNA between lung tumor tissue and normal lung tissue. Therefore, it follows that the PRO1158 gene, polypeptide, and antibody can be used to distinguish lung tumor tissue from normal lung tissue. The Examiner has not offered any significant arguments or evidence to the contrary, and therefore has not established a *prima facie* case that one of skill in the art would reasonably doubt the asserted utility.

b. The lack of a known role for PRO1158 in tumor formation or the development of cancer does not prevent its use as a diagnostic tool for cancer

Appellants turn next to the Examiner's argument that paragraph 4 of the second Grimaldi declaration (originally submitted as Exhibit 2 with the Appellants' Amendment and Response to Office Action) was not persuasive because unlike the genes discussed in the references cited in the declaration, "[t]he PRO1158 gene, ... has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, ... no translocation of PRO1158 is known to occur. ... No mutation or translocation of PRO1158 has been associated with lung cancer." *Final Office Action* at 4. The Examiner concluded that "[i]n the absence of any of the above information" the disclosure was insufficient to satisfy the requirements of § 101. *Id.*

The Examiner's arguments fail to establish that one of skill in the art would doubt Appellants' asserted utility. Once again, the Examiner has failed to establish how the "absence of any of the above information" is relevant to the asserted utility. The lack of a known role for PRO1158 in tumor formation or the development of cancer does not prevent its use as a diagnostic tool for cancer. Likewise, the fact that there is no known translocation or mutation of PRO1158 is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1158 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue.

The Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (See the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Appellants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Appellants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. *See, e.g.,* U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343.

In addition, Appellants note that they did not even rely on the portion of the second Grimaldi declaration cited by the Examiner. Instead, Appellants submitted the second Grimaldi declaration in support of the assertion that changes in mRNA are positively correlated to changes in protein levels. Appellants relied on paragraph 5 of the declaration which states: "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." *Response to Final Office Action* at 11, quoting *Second Grimaldi Declaration* at ¶ 5. As support for this statement, Mr. Grimaldi noted that "[t]echniques used to detect mRNA, such as Northern Blotting, Differential Display, *in situ* hybridization, quantitative PCR, Taqman, and more recently Microarray technology all rely on the dogma that a change in mRNA will represent a similar change in protein. If this dogma did not hold true then these techniques would have little value and not be so widely used." *Second Grimaldi Declaration* at ¶ 5. Whether the differential expression of mRNA is due to mutations or translocations has no bearing on the portion of the Grimaldi reference relied on by Appellants. The Examiner did not even address this portion of the second Grimaldi declaration until the Advisory Action.

c. The sole reference cited by the Examiner does not support the rejection of the pending claims

Appellants turn next to Examiner's final argument and the sole reference cited by the Examiner to support her rejection.[1] In the Advisory Action, the Examiner cites Chen *et al.* as support for the assertion that the correlation between protein levels and mRNA expression in lung adenocarcinomas varies depending on the protein. The authors of the Chen reference examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and nine non-tumor lung samples.

As an initial matter, it is important to note that a portion of Chen is clearly not relevant to Appellants' assertion that changes in the level of mRNA lead to changes in the level of the encoded polypeptide. In one experiment, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of

all the samples for each gene or protein, and then looked for a correlation across different genes. Based on these data, Chen reported that "no significant correlation between mRNA and protein expression was found (r = -0.025) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes)." *Chen* at Abstract. This measurement of a correlation across genes is not relevant to Appellants' asserted utility, and is apparently not relied on by the Examiner.

Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 17% (28 of 165) of the protein spots, or 21.4% (21 of 98) of the genes, showed a statistically significant correlation between protein and mRNA expression. *Chen* at Abstract. It is these results that the Examiner relies on for support.

However, read in its entirety, Chen provides scant evidence to counter Appellants' asserted utility because portions of Chen support Appellants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells.

Appellants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Appellants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Appellants' assertion that there is a correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The Examiner relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support her assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, as is explained below, the apparent lack of a correlation cannot be used as evidence that Appellants' assertion of a general correlation is wrong.

To determine if there is a correlation between changes in mRNA and changes in protein levels, one would have to conduct experiments where a measurable change in mRNA for a

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[1] Appellants question the propriety of citing a reference for the first time in an Advisory Action since they were afforded no opportunity to respond to the cited reference. Therefore, Appellants

particular gene is observed, and then examine if there was a corresponding change in the level of the corresponding protein. Stated differently, if there was no substantial change in mRNA levels for a particular gene, one cannot measure a correlation between changes in mRNA and changes in the encoded protein for that gene. Therefore, one must know if the individual genes studied by Chen were differentially expressed to know if the observed lack of correlation has any relevance to Appellants' assertions of a general correlation between changes in mRNA and protein.

Importantly, unlike Appellants, Chen did not examine differences in mRNA between tumor and normal tissue where one would expect to find substantial changes in the level of mRNA for certain genes. Instead, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level. *Chen* at 306, right column. Therefore, it is not known if there was any substantial difference in mRNA levels for the various studied genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Appellants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis. Since almost all samples tested by Chen were from the same type of tissue, one would expect most genes examined by Chen to have similar mRNA or protein levels across the samples. In the absence of substantial differential expression, no correlation would be observed. Because it is not known if there was a change in the level of the genes studied by Chen, *i.e.* whether they were differentially expressed, the lack of an observed correlation cannot be used to counter Appellants' assertion.

In sum, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Appellants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, these data explain the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen – there is no indication the genes are differentially expressed. Thus, Chen's results do not refute Appellants' position. Instead, Chen supports Appellants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater.

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must present their response to the cited reference for the first time here.

In further support of Appellants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Appellants' asserted utility, as the Examiner has apparently acknowledged, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the Examiner's position.

Given the fact that portions of Chen as well as the relevant references cited by Chen support Appellants' position, and the remainder of Chen cannot be relied on as contrary to the Appellants' position, the Examiner has failed to establish a *prima facie* case that one of skill in the art would doubt Appellants' asserted utility.

d. Conclusion – Examiner has failed to establish a Prima Facie case that one of skill in the art would doubt Appellants' asserted utility

The Examiner has relied on essentially three unsupported arguments in rejecting the pending claims for lack of utility. First, the Examiner has questioned the sufficiency, reliability and significance of the data reported in Example 18 as well as the supporting first Grimaldi declaration. Second, the Examiner has argued that absent some known translocation or mutation of PRO1158, or some role for PRO1158 in cancer formation or development, the disclosure is insufficient. Finally, in the Advisory Action, the Examiner relies on Chen *et al.* for the first time to support the assertion that it cannot be assumed that mRNA levels correlate to protein levels. Appellants have responded to each of these arguments in turn.

First, Appellants have shown that the data in Example 18 are sufficient to show that PRO1158 is useful as a cancer diagnostic tool. This assertion is supported by the first Grimaldi declaration. The Examiner has not provided any substantial reason or evidence for one of skill in the art to doubt the reliability or usefulness of Example 18, or the facts and conclusions in the first Grimaldi declaration.

Second, Appellants have shown that the lack of a known translocation or mutation of PRO1158, or the lack of a known role for PRO1158 in the formation or development of cancer is not required to use PRO1158 as a diagnostic tool. One does not need to know why PRO1158 is

differentially expressed in certain tumors, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue.

Finally, Appellants have shown that portions of Chen *et al.*, as well as some of the references cited by Chen, actually support Appellants assertion that changes in mRNA levels generally correlate with changes in the level of the encoded polypeptide. The remainder of Chen is not reliable enough to offer any support for the Examiner's position.

Taken together, the Examiner's arguments are not sufficient to satisfy the Examiner's burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Examiner's arguments are conclusory statements which are not supported by any evidence or reasoning which explains why one of ordinary skill in the art would reasonably doubt the asserted utility. Therefore, the Board should accept the Appellants' disclosure of utility. *See Ex parte Rubin*, 5 U.S.P.Q. 2d 1461 (Bd. Pat. App. & Interf. 1987) ("There is no factual support in this record for the examiner's questioning of the denaturation test reported in the specification. ... No reason to doubt 'the objective truth' of the asserted utility having been advanced by the examiner, we accept appellant's disclosure of utility corresponding in scope to the claimed subject matter.").

7. ***Appellants have provided Sufficient Rebuttal Evidence of Utility***

"Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Appellant to provide rebuttal evidence." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The rebuttal evidence must be sufficient such that when it is considered as a whole, it is more likely than not that the asserted utility is true. *See In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992) (stating that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard). The M.P.E.P. summarizes the standard of proof required:

> [T]he Appellant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the Appellant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is

> more likely than not true. M.P.E.P. at § 2107.02, part VII (emphasis in original, citations omitted).

Appellants remind the Board that the Federal Circuit has stated that the standard for satisfying the utility requirement is a low one: "The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q. 2d 1700 (Fed. Cir. 1999).

Even if the Examiner has satisfied her burden of presenting a *prima facie* case of lack of utility, Appellants have supplied more than enough rebuttal evidence, such that when considered as a whole, one of skill in the art would conclude that the asserted utility is more likely than not true. Appellants have provided sufficient evidence that the gene encoding the PRO1158 polypeptide is differentially expressed in lung cancer and can therefore be used as a diagnostic tool. In addition, Appellants have shown that it is well established in the art that there is a reasonable correlation between changes in mRNA level and changes in the corresponding protein level such that one of skill in the art would believe that the PRO1158 polypeptide is also differentially expressed in certain cancers. Therefore, considering the evidence as a whole, one of skill in the art would believe that it is more likely than not that the claimed antibodies are useful as diagnostic tools for cancer, particularly lung tumors.

a. Appellants have established that the gene encoding the PRO1158 polypeptide is differentially expressed in certain cancers

As discussed above, the Examiner has not provided any evidence to challenge the reliability and significance of the data in Example 18 which reports that the mRNA for PRO1158 is more highly expressed in normal lung tissue compared to lung tumor. In contrast to this complete lack of evidence on the part of the Examiner, Appellants have submitted the first Grimaldi declaration. That declaration establishes that it is the opinion of an expert in the field who has personal knowledge of the facts surrounding Example 18 that there is at least a two-fold difference in mRNA for PRO1158 between the tumor tissue and the counterpart normal tissue, and that the PRO1158 genes, polypeptides and antibodies are useful for differentiating tumor tissue from normal tissue. The Examiner has not provided any evidence to challenge the facts and conclusions of the first Grimaldi declaration in support of Example 18.

Given the disclosure of Example 18 and the supporting first Grimaldi declaration on the one hand, and the complete lack of any evidence on the other, it is clear that considering the evidence as a whole, one of skill in the art would conclude that it is more likely than not that the PRO1158 gene is differentially expressed in lung tumor compared to normal lung tissue such that is useful as a diagnostic tool to distinguish tumor tissue from normal tissue.

As Appellants explain below, it is more likely than not that the PRO1158 polypeptide is also differentially expressed in lung tumor tissue, and can therefore be used to distinguish tumor tissue from normal tissue. This provides utility for the claimed antibodies to the PRO1158 polypeptide.

b. Appellants have established that generally there is a correlation between changes in mRNA expression levels and changes in the expression level of the encoded protein

Appellants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that in most cases a change in the level of mRNA for a particular protein leads to a corresponding change in the level of the encoded protein. Given Appellants' evidence of differential expression of the mRNA for the PRO1158 polypeptide in lung tumor, it is more likely than not that the PRO1158 polypeptide is likewise differentially expressed, and therefore the claimed antibodies are useful as diagnostic tools, particularly for lung tumors.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Appellants submitted a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." *Second Grimaldi Declaration* at ¶ 5. Further, "increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression." *Id.*

Appellants also submitted the declaration of Paul Polakis, Ph.D. an expert in the field of cancer biology (attached as Exhibit 3 to Appellants' Amendment and Response to Office Action). As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases studied in relation to the present invention] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." *Polakis Declaration* at ¶ 6.

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted with Appellants' After Final Amendment as Exhibit 1, hereinafter "Cell 3rd") and (4th ed. 2002) (submitted with Appellants' After Final Amendment as Exhibit 2, hereinafter "Cell 4th")). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." *Cell 3rd* at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." *Cell 3rd* at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA.*" *Cell 4th* at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from

gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." *Cell 4th* at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." *Cell 4th* at 379 (emphasis added).

Further support for Appellants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted with Appellants' After Final Amendment as Exhibit 3) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (submitted with Appellants' After Final Amendment as Exhibit 4). Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" *Zhigang* at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." *Id.* at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), (submitted with Appellants' After Final Amendment as Exhibit 5), states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. *Meric et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references discussed above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and changes in the level of the encoded protein. In contrast to this substantial amount of evidence supporting Appellants' position, the Examiner has cited a single reference, Chen *et al.* However, as discussed above, portions of Chen and the relevant references cited by Chen actually support Appellants' position, and the remainder of Chen is inconclusive. It is clear that when considered as a whole, the preponderance of the evidence clearly weighs in favor of Appellants.

Appellants have presented sufficient evidence to establish that the mRNA for PRO1158 is differentially expressed in lung tumor tissue compared to normal lung tissue, and that it is more likely than not that this leads to differential expression of the PRO1158 polypeptide. This makes the claimed antibodies to PRO1158 polypeptide useful for diagnosing cancer, particularly lung cancer. Given the overwhelming amount of evidence in support of Appellants' position, and the near absence of any evidence in support of the Examiner's position, when considered as a whole the evidence leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

8. *The Courts have held that the Utility Requirement was Satisfied in Similar Cases*

The seminal decision interpreting the utility requirement of 35 U.S.C. § 101 is *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. 689 (1966). At issue in *Brenner* was a claim to "a chemical process which yields an already known product whose utility – other than as a possible object of scientific inquiry – ha[d] not yet been evidenced." *Id.* at 529, 148 U.S.P.Q. at 693. The Patent Office rejected the claimed process for lack of utility because the product produced by the claimed process had no known use. *See id.* at 521-22, 148 U.S.P.Q. at 690. On appeal, the Court of Customs and Patent Appeals reversed, holding "where a claimed process produces a known product it is not necessary to show utility for the product." *Id.* at 522, 148 U.S.P.Q. at 691.

In reviewing the lower court's decision, the Court made its oft quoted statement that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point – where specific benefit exists in currently available form – there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field." *Id.* at 534-35, 148 U.S.P.Q. at 695.

The first opinion of the C.C.P.A. applying *Brenner* was *In re Kirk*, 376 F.2d 936, 153 U.S.P.Q. 48 (C.C.P.A. 1967). The invention claimed in *Kirk* was a set of steroid derivatives said to have valuable biological properties and to be of value "in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice." *Id.* at 938, 153 U.S.P.Q. at 50. In affirming the claim rejection based on a lack of utility, the court held that the "nebulous expressions 'biological activity' or 'biological properties'" did not adequately convey how to use the claimed compounds. *Id.* at 941, 153 U.S.P.Q. at 52. The court also rejected Appellants' supporting affidavit, stating, "the sum and substance of the affidavit appears to be that one of ordinary skill in the art would know 'how to use' the compounds to find out in the first instance whether the compounds are – or are not – in fact useful or possess useful properties, and to ascertain what those properties are." *Id.* at 942, 153 U.S.P.Q. at 53.

Since these early decisions, the courts have continued to clarify what is sufficient to satisfy the utility requirement. Three more recent decisions are of particular relevance to the instant application: *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996).

The earliest of these cases, *Nelson v. Bowler*, involved an interference between two applications related to derivatives of naturally occurring prostaglandins (PG). *Nelson*, 626 F.2d at 854-55. The issue was whether Nelson had shown at least one utility for the compounds at issue to establish an actual reduction to practice. *Id.* at 855. The Appellants relied on two tests to prove practical utility: an *in vivo* rat blood pressure (BP) test and an *in vitro* gerbil colon smooth muscle stimulation (GC-SMS) test. In the BP test, the blood pressure of anesthetized rats was recorded on a polygraph chart to determine whether an injected compound had any effect. Responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect.

Id. In the GC-SMS test a section of colon was excised from a freshly-killed gerbil for suspension in a physiological solution, and a lever arm was connected to the colon in such a way that any contraction was recorded as a polygraph trace. *Id.* The Board held that Nelson had not shown adequate proof of practical utility, characterizing the tests as "rough screens, uncorrelated with actual utility." *Id.* at 856.

On appeal the C.C.P.A. reversed, holding that the Board "erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use." *Id.* The Court stated that "practical utility" was characterized as a use of the claimed discovery in a manner which provides some immediate benefit to the public, establishing the following rule:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of <u>any</u> such activity constitutes a showing of practical utility. *Id.* (emphasis added).

The Court rejected Bowler's argument that the BP and GC-SMS tests are inconclusive showings of pharmacological activity since confirmation by statistically significant means did not occur until after the critical date. The Court stated that "a rigorous correlation is <u>not necessary</u> where the test for pharmacological activity is <u>reasonably indicative</u> of the desired response." *Id.* (emphasis added). The Court concluded that a "<u>reasonable correlation</u>" between the observed properties and the suggested use was sufficient to establish practical utility. *Id.* at 857.

The sufficiency of a "reasonable correlation" in establishing utility was affirmed by the Court of Appeals for the Federal Circuit in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the subject of the interference before the Court was imidazole derivative compounds which inhibit the synthesis of thromboxane synthetase, an enzyme which leads to the formation of thromboxane A_2. At the time the applications were filed, thromboxane A_2 was postulated to be involved in platelet aggregation, which was associated with several deleterious conditions. *Id.* at 1042.

The question before the Board and reviewed by the Court was whether Iizuka was entitled to the benefit of his Japanese priority application. *Id.* The Japanese application disclosed that

the imidazole derivatives showed strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, an *in vitro* utility. *Id.* at 1043. Relying in part on *Nelson,* the Board held that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use, and concluded that the *in vitro* tests were sufficient to establish a practical utility. *Id.*

On appeal, Cross argued that the basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds, and that more sophisticated *in vitro* or *in vivo* tests were necessary to establish a practical utility. *Id.* at 1050. The Court rejected this argument, noting that adequate proof of any pharmaceutical activity constitutes a showing of practical utility. *Id.* The Court accepted the argument that initial testing of compounds is widely done *in vitro*:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Iizuka has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, Iizuka's position is that successful *in vitro* testing for a particular pharmacological activity establishes a significant probability that *in vivo* testing for this particular pharmacological activity will be successful. *Id.* (emphasis added).

The Court also noted that in previous decisions, its predecessor court had accepted evidence of *in vivo* utility as sufficient to establish practical utility. The Court reasoned that:

> This *in vivo* testing is but an intermediate link in a screening chain which may eventually lead to the use of the drug as a therapeutic agent in humans. We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility. *Id.* at 1051, *citing Nelson,* 626 F.2d at 856 (emphasis added).

Based on this reasoning, the Court affirmed the decision of the Board, stating that "based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *Id.* at

1050 (emphasis added). The Court therefore held that the disclosed *in vitro* utility was "sufficient to comply with the practical utility requirement of § 101." *Id.* at 1051.

The holdings of *Nelson* and *Cross* were more recently affirmed in *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996). In *Fujikawa*, the Court again affirmed the notion that initial screens of compounds provide a practical utility even though they may not provide a therapeutic use because "'[i]t is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities.'" *Id.* at 1564, *quoting Nelson,* 626 F.2d at 856. The Court noted that it may be difficult to predict whether novel compounds will exhibit pharmacological activity, and consequently testing is often required to establish practical utility. *Id.* However the Court went on to state:

> But the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior." *Id.* (internal citations omitted, underline emphasis added, italics in original).

On appeal, Fujikawa argued that Wattanasin had failed to establish an adequate correlation between the *in vitro* and *in vivo* results to permit Wattanasin to rely on positive *in vitro* results to establish a practical utility. The Court stated that the Board relied on testimony from those skilled in the art that the *in vitro* results convinced the experts that the claimed compounds would exhibit the desired pharmacological activity when administered *in vivo*, including testimony that *in vivo* activity is typically highly correlatable to a compound's *in vitro* activity in the field. *Id.* at 1565. To overcome this evidence and counter the Board's decision, Fujikawa pointed to the testimony of its expert that "there is a reasonable element of doubt that some elements may be encountered which are active in the *in vitro* assay, but yet inactive in the *in vivo* assay." *Id.*

The Court rejected this argument: "Of course, it is possible that some compounds active *in vitro* may not be active *in vivo.* But, as our predecessor court in *Nelson* explained, a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices." *Id.* (emphasis added). The Court also rejected Fujikawa's reliance on two articles.

The Court noted that while one article taught that "*in vitro* testing is sometimes not a good indicator of how potent a compound will be *in vivo,* it does imply that compounds which are active *in vitro* will normally exhibit some *in vivo* activity." *Id.* at 1566. Similarly, the Court noted that the second article expressly stated that "[f]or most substances, although not for all, the relative potency determined in *in vitro* ... parallels the *in vivo* activity." *Id.*

The Court concluded that the facts in the case were analogous to the ones in *Cross* where the court relied on a known reasonable correlation between *in vitro* tests and *in vivo* activity, and therefore affirmed the Board's decision that Wattanasin had established a practical utility with the *in vitro* results. *Id.* at 1565-66.

The *Nelson*, *Cross*, and *Fujikawa* cases are very similar to the present case. The reasoning of the courts in all three cases that "'[i]t is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities'" applies to the asserted utility for the claimed antibodies. *Fujikawa*, 93 F.3d at 1564, *quoting Nelson,* 626 F.2d at 856; *see also Cross*, 753 F.2d at 1051 ("Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility."). Like pharmaceutical compounds, nucleic acids, polypeptides, and antibodies which are associated with cancer will make it inherently faster and easier to combat cancer. The greater the number of biological markers of cancer medical professionals have access to, the more accurate and detailed a diagnosis they can make. The determination that a gene is differentially expressed in cancer constitutes at least as significant a development in the field of cancer diagnostics as *in vitro* screening for pharmaceutical activity. *See Cross*, 753 F.2d at 1051 ("the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public.").

In addition, like *in vitro* tests in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see discussion supra). Were there no reasonable correlation between the two, the

techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. *See Second Grimaldi Declaration* at ¶ 5. As in *Cross*, Appellants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. *See Cross*, 753 F.2d at 1050. Instead, Appellants' position detailed above is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween." *Id.*; *see also Fujikawa*, 93 F.3d at 1565 ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Nelson*, 626 F.2d at 857 (holding that "a rigorous correlation is not necessary" and that a "reasonable correlation" will suffice).

Also of importance is the Court's rejection of the notion that any *in vitro* testing must be statistically significant to support a practical utility. *Nelson*, 626 F.2d at 857. Likewise, qualitative characterizations of a test compound as either increasing or decreasing blood pressure was acceptable. *Id.* at 855 (stating that responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect). This is similar to the data in Example 18, where the change in mRNA levels is described as "more highly expressed."

There are additional similarities. In *Fujikawa*, the Board and Court rejected the argument that there was no utility because there was no exact correlation between the *in vitro* and *in vivo* results in spite of supporting testimony and references. *Fujikawa*, 93 F.3d at 1565-66. Like the two references rejected by the Board and Court in *Fujikawa*, the Chen *et al.* reference cited by the Examiner may suggest that the correlation between changes in mRNA levels and protein levels is not exact. But like *Fujikawa*, portions of Chen *et al.* also support Appellants' assertion, and Appellants have submitted the declaration of two experts in the field which state that those in the field rely on the correlation between changes in mRNA and protein. *See Second Grimaldi Declaration* at ¶ 5; *Polakis Declaration* at ¶ 6. Thus, as was the case in *Fujikawa*, although there may be some evidence that the correlation relied on is not exact, the declarations and numerous references submitted by Appellants is more than enough evidence to establish that there is a "reasonable correlation" between changes in mRNA levels and changes in the level of the encoded protein.

In conclusion, Appellants have asserted that the claimed antibodies are useful for the diagnosis of cancer, particularly lung cancer based on the data in Example 18. This utility is far beyond the nebulous expressions "biological activity" or "biological properties" rejected in *In re Kirk*, 376 F.2d 936, 153 U.S.P.Q. 48 (C.C.P.A. 1967). Like *Nelson*, *Cross*, and *Fujikawa*, Appellants have asserted a utility which relies on a reasonable correlation between the data disclosed in the application and the asserted utility. The fact that there may be limited evidence that the correlation is not exact does not invalidate Appellants' showing of utility since the correlation need not be a rigorous or exact one. Considering the relevant evidence as a whole, Appellants have provided sufficient evidence to establish a reasonable correlation between changes in the level of mRNA and corresponding changes in the level of the encoded polypeptide. Therefore the claimed antibodies have a practical utility as diagnostic tools for lung cancer.

9. ***Utility – Conclusion***

Appellants' asserted utility for the claimed antibodies as diagnostic tools for cancer corresponds in scope to the subject matter sought to be patented and therefore "must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). The Examiner's unsupported arguments and single inconclusive reference are not sufficient evidence to make a *prima facie* showing that "one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). And even if the Examiner has established a *prima facie* case, Appellants have offered sufficient rebuttal evidence in the form of expert declarations and references, which, when considered as a whole, establish that it is more likely than not that the asserted utility is true. *See In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992) (stating that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard); *M.P.E.P.* at § 2107.02, part VII ("evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.") (emphasis in original). Finally, the courts' decisions in similar cases make clear that the evidence provided by Appellants is sufficient to establish the

asserted utility. The evidence does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa*, 93 F.3d at 1565 ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross*, 753 F.2d at 1050 (same); *Nelson*, 626 F.2d at 857 (same). Considering the evidence as a whole in light of the relevant cases, the Board should find that Appellants have established at least one specific, substantial, and credible utility, and the Examiner's rejection of the pending claims as lacking utility should be reversed.

B. Enablement Rejection

The second issue before the Board is whether Appellants have enabled the pending claims such that one of skill in the art would be able to make and use the claimed invention. The Examiner has rejected Claims 1-5 under 35 U.S.C. §112, first paragraph, arguing that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art clearly would not know how to use the claimed invention. *See First Office Action* at 4; *Final Office Action* at 5; *Advisory Action* at 2.

1. ***Because the Claimed Invention is Supported by a Specific, Substantial and Credible Utility, the Enablement Rejection should be Reversed***

For the reasons stated above, the claimed invention is supported by a specific, substantial and credible utility. Because the lack of a supporting utility is the only basis for the Examiner's rejection under 35 U.S.C. § 112, first paragraph, the Board should reverse the rejection of Claims 1-5 as lacking enablement.

C. Conclusion

In view of the arguments presented above, Appellants submit that the specification as filed provides a specific, substantial and credible utility for the claimed antibodies and request withdrawal of the rejection under 35 U.S.C. §101, and the related rejection under 35 U.S.C. §112.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 5, 2005

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VIII. APPENDIX A – Claims on Appeal

1. An isolated antibody that specifically binds to the polypeptide of SEQ ID NO: 68.
2. The antibody of claim 1 which is a monoclonal antibody.
3. The antibody of claim 1 which is a humanized antibody.
4. The antibody of claim 1 which is an antibody fragment.
5. The antibody of claim 1 which is labeled.

IX. APPENDIX B – Evidence

Attached hereto is a copy of the evidence cited in Appellants' Brief. The list of evidence below is accompanied by a statement setting forth where in the record that evidence was entered into the record by the Examiner.

X. APPENDIX C – Related Proceedings

There are no decisions rendered by a court or the Board in any related proceedings identified above.